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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/677,496	10/03/2003	Milan S. Blake	38777-0059	4551

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EXAMINER	
LUCAS, ZACHARIAH	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 11/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/677,496	BLAKE ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *7-9 and 11-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9-22-04, 10-2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group II (claims 1-6 and 10 as they are drawn to methods for enhancing the production of bacterial toxins through growth of the bacteria in a culture medium that is deficient in sulfate ion metabolic precursor), and subgroup (A) wherein the bacteria are Bordetella, in the reply filed on September 22, 2004 is acknowledged. The traversal is on the ground(s) that there would be no undue burden on the examination of the different inventions in a single application. This is not found persuasive because each of the methods claimed involves either a different mode of operation, a method of producing a different toxin, or both. Thus, the search and examination of one of the claimed methods would not be coextensive, or sufficient to determine the patentability, of the others.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 7-9, and 11-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on September 22, 2004.

3. Claims 1-6 and 10 are under consideration to the extent that they read on, or are generic to, methods of enhancing the production of Bordetella toxins by culturing the bacteria in a medium deficient in sulfate ion metabolic precursors.

Priority

4. Applicants claim for priority to prior application 09/825,770 and 60/194,482 is noted.

With respect to the claim to 09/825770, it is noted that this application has not been published as U.S. Patent 6,686,180. Where an applicant desires priority under 35 U.S.C. 120 to a previously filed application, specific reference to the earlier filed application must be made in the instant application. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications. **The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included.** If the parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph unless it appears in an application data sheet.

Applicant is additionally required to amend the reference to provisional application 60/194,482 such that the reference reads - - this application is a divisional of application 09/825,770, filed on April 4, 2001, now U.S. Patent 6,686,180, which claims benefit of U.S. Provisional Application 60/194,482, filed on April 4, 2000- -. See, MPEP § 201.11 III.

5. It is noted that the present application claims priority as a divisional to prior non-provisional application 09/825,770, filed on April 4, 2001, and through that application to provisional application 60/194,482, filed on April 4, 2000. However, it is also noted that the provisional application does not appear to provide written description support for the currently claimed inventions- methods of increasing bacterial toxin production by culturing the bacterial

cells in a media with reduced cysteine concentration. Thus, the Applicant is not awarded priority to the April 4, 200 date with respect to the elected invention.

Information Disclosure Statement

6. The information disclosure statements (IDS) submitted on October 3, 2003 and on September 22, 2004 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner.

Claim Objections

7. Claim 2 is objected to because of the following informalities: the claim provides a list of alternative members, but does not include a comma separating the last and next to last members.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-6 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims read on methods of increasing the production of a bacterial toxin by reducing toxin expression inhibitors, or by providing a reduced concentration of sulfate ion metabolic precursors. These claims read on involving "reduced" concentrations of indicated compounds. The term “reduced” is a relative term which renders the claim indefinite. The term "reduced" is not defined by the claim, the specification does not provide a standard for

ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear what the Applicant considers to be a reduced concentration of an inhibitor or sulfate ion metabolic precursor as the application does not provide a standard basis for comparison. The claims are therefore rejected as being indefinite.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-6 and 10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to a genus of methods comprising the production of any bacterial toxins through the cultivation of bacteria in a media deficient in any metabolic precursor to any toxin expression inhibitor.

The following quotation from section 2163 of the Manual of Patent Examination Procedure is a brief discussion of what is required in a specification to satisfy the 35 U.S.C. 112 written description requirement for a generic claim covering several distinct inventions:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics,

> sufficient to show the applicant was in possession of the claimed genus... See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

Thus, when a claim covers a genus of inventions, the specification must provide written description support for the entire scope of the genus. Support for a genus is generally found where the applicant has provided a number of examples sufficient so that one in the art would recognize from the specification the scope of what is being claimed.

In the present case, the claims are drawn to a genus of enhancing the production of 1) any bacterial toxin through 2) culturing the bacteria in a media deficient in any metabolic precursor of 3) any toxin expression inhibitor. Each of these elements requires a description of a genus of compounds. In the present case, the application has defined only a single inhibitor (sulfate) of a single bacterial toxin (the pertussis toxin- PT). Pages 24-26. Further, the applicant has identified only a single metabolic precursor of the sulfate ion- cysteine. Id. There is no identification of any other toxin expression inhibitors to PT or any other toxin, no identification of more than the single precursor of that one inhibitor. Additionally, there are no examples demonstrating that the identified PT expression inhibitor also inhibits expression of other bacterial toxins. Thus, the Applicant has disclosed only a single working example of the claimed methods.

While the Applicant need not necessarily disclose multiple species, the Applicant must support the claimed inventions through identification of the invention through more than functional language. In the instant, the identification of a structural or chemical characteristic common to toxin expression inhibitors, or to metabolic precursors of such, that correlates with the function would be an example of a possible alternative basis for support. However, no such

description is provided in the application. Nor does such a description appear to be disclosed in the art.

Because the Applicant has provided only a single example of the claimed invention, and because the application does not provide any alternative means of identifying toxin expression inhibitors or their metabolic precursors other than by function, the Applicant has not provided adequate written description support for the claimed methods.

12. Claims 1-6, and 10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of enhancing the production of the PT toxin comprising cultivation of B. pertussis in a cysteine deficient media, does not reasonably provide enablement for methods of enhancing the expression of any bacterial toxin through the cultivation of the bacteria in a media wherein the presence of any toxin expression inhibitor has been eliminated or reduced, or for enhancing the production of any toxin wherein the media is deficient for sulfate ion metabolic precursors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The claims have been described above. For the purposes of this rejection, it is assumed that the Applicant is enabled for methods of cultivating Bordetella bacteria in cysteine deficient media.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary,

(2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

The claims are broadly drawn to methods of increasing the production of any bacterial toxin through the culturing of the respective bacterial cells in a culture media deficient in a sulfate ion metabolic precursor. The application indicates that cysteine is a precursor of sulfate ions. Additionally, the teachings of the application demonstrate that culture media with reduced cysteine is able to increase the production of PT by B. pertussis. However, the application does not provide evidence that the same culture media can yield increased production of any other toxins, provide any guidance as to what other toxins would be similarly affected by the reduced cysteine, or demonstrate that any metabolic precursor to sulfate would be able to increase production in PT or in any other bacterial toxin. Thus, in contrast to the breadth of the claims, the application provides examples of only a single embodiment of the claimed methods, and provides no guidance as to what, if any, other sulfate metabolic precursors may be depleted to achieve the desired affect, or as to what, if any, other toxins may achieve an increased yield when such depleted media are used.

It is noted that certain references in the art also provide teachings regarding the effect of cysteine on bacterial toxin (i.e. PT) production. See, Bogdan et al. Infect Immun 69: 6823-60, and Stenson et al., Infect Immun 71: 1316-20. Like the teachings of the present application, each of these references indicates that the effect of cysteine on toxin production is due to the

interaction of the cysteine metabolite with the intracellular biochemistry of the Bordetella pathogen. However, there has been no demonstration, nor any suggestion, that the effects seen in the Bordetella cells would be representative to those of any toxin producing bacterium. In view of the large number of bacteria, and bacterial toxins, the differences in their metabolic and intracellular functions, and the lack of any data demonstrating that B. pertussis is representative of all bacteria, the Applicant has not provided sufficient information to enable those in the art to practice the claimed invention to the full scope.

It is also noted that other references in the art have provided teachings that cysteine is involved with the inhibition of other pathogenic proteins and toxins. See, Karlsson et al., Infection and Immunity, 68: 5881-88; and Lisker et al., Can J Microbiol 31: 973-76. However, while these references indicate that cysteine is able to inhibit toxin production in certain other specific pathogens, neither of the references suggests that cysteine is generally useful to inhibit toxin production, nor do these references attribute the inhibitory activity on the production of sulfate. See esp., Lisker (stating explicitly on page 975 that "cysteine (as a sulfur source) had no effect on ochratoxin production," and continues by indicating that the amino acid's inhibitory activity in that instance was due to its use as a nitrogen source). The teachings of Karlsson also fail to support a conclusion that cysteine is generally useful to inhibit pathogenic toxin production. Rather, the reference limits its teachings to the effect of cysteine on C. difficile toxins, thereby indicating that those in the art generally do not assume that data regarding one bacterial pathogen apply to bacterial cells generally. Additionally, the reference does not attribute the inhibitory activity on the amino acid's status as a metabolic precursor for sulfate. Thus, while the art supports the Applicant's assertion that the claimed method may be applied to

the production of other bacterial pathogens, there is still insufficient data to indicate that a reduction of cysteine in a culture media would be effective to increase the production of toxins for any bacteria. Additionally, the art does not support the teachings that any metabolic precursor of sulfate ions would be so useful.

13. Claims 1-6 and 10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of enhancing the production of PT by culturing B. pertussis in a culture media comprising a reduced concentration of cysteine, does not reasonably provide enablement for methods wherein the culture media is deficient in cysteine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The claims read on methods of enhancing the production of bacterial toxins through cultivation of the bacteria in media with reduced or eliminated toxin expression inhibitors. The elected invention is drawn to methods wherein the bacteria Bordetella.

The application discloses that the Bordetella bacteria produce two toxins, pertussis toxin (PT) and pertactin. As described above, the application demonstrates that the addition of certain compounds that inhibit the activity of sulfate ions leads to increased expression of PT. See e.g., pages 25-26. Additionally, the application provides experimental evidence that culture media with reduced cysteine concentrations resulted in increased PT production. See, pages 8-13. However, the application does not demonstrate the use of a cysteine deficient culture media.

With respect to the use of culture media that are deficient in cysteine, the art indicates that the application is not enabling. Two references, each of which deal with the same art as the

claimed methods, each indicate that the presence of some form of cysteine is a requirement for the growth Bordetella cells, and the expression of PT. See, Bogdan et al. Infect Immun 69: 6823-60, and Stenson et al., Infect Immun 71: 1316-20. Both of these references indicate that, in the absence of cysteine (from some source) no cell growth or protein synthesis was seen. See e.g., Stenson, abstract (stating "Cysteine is an essential amino acid for B. pertussis and must be present for protein synthesis and bacterial growth"); and Bogdan, page 6827 (teaching that cysteine was required for the growth of the bacteria in culture). In view of these teachings, and the lack of any demonstration in the application that the bacteria can produce increased quantities of PT when cultured in cysteine deficient media from that produced in normal culture media, the Applicant is not enabled for methods wherein the culture media is cysteine deficient.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 1, 5, 6, and 10 are rejected under 35 U.S.C. 102(a) as being anticipated by Karlsson et al., Infection and Immunity, 68: 5881-88. These claims read on methods of enhancing the production of bacterial toxins by culturing the bacteria in media comprising reduced concentrations of sulfate ion metabolic precursors- wherein cysteine is identified as such

a precursor. Karlsson teaches the culturing of C. difficile in media comprising different concentrations of cysteine, and that those media comprising lower concentrations resulted in increased toxin production. Page 5882, esp. section titled "Cysteine and cysteine derivatives down-regulate toxin production in dose-dependent manner." The reference therefore anticipates the indicated claims.

It is noted that the reference does not teach that sulfate ions are responsible for the inhibition of toxin production as is described in claim 5. However, this claim is merely describing an intended mode of operation, and does not appear to further identify the steps of the claimed method. In particular, this limitation is not inconsistent with the later identification of the claimed methods as involving the use of a reduced concentration of cysteine. Thus, this claim does not appear to distinguish the claimed methods from those of the prior art.

16. Claims 1-5 are rejected under 35 U.S.C. 102(b) as being anticipated by either of Quentin-Millet et al. (U.S. Patent 4,965,205), or Sekura et al. (U.S. Patent 5,338,670), issued to Sekura et al. The rejected claims describe a method for enhanced production of bacterial toxins, including the pertussis toxin of the Bordetella pertussis bacterium, wherein the method comprises cultivating the bacterium in a bacterial culture media in which toxin expression inhibitors have been eliminated or reduced. The present application teaches that one means by which this is accomplished is through the inclusion in the media of certain metal salts. Pages 3, paragraph [0011].

Quentin-Millet teaches the use of a culture medium containing metal salts for the culturing of Bordetella pertussis. Col. 1, lines 10-20, and 59-66. It further teaches that using the

culture medium assisted in the expression of the pertussis toxin antigens. Col. 3, lines 18-25. Although the reference does not disclose the purpose of the metal salts, or that the salts formed complexes with sulfate ions, the activity of the salts would be inherent in the use of the culture media comprising them. This reference therefore anticipates the stated claims.

Sekura also teaches the use of a bacterial culture medium comprising metallic salts. Col. 4, lines 32-45. The method disclosed, wherein B. pertussis is being cultivated for the co-expression of the pertussis toxin, inherently indicates that the culture medium components are intended to increase pertussis toxin yield. As the culture medium comprises the metallic salts, and is used for the cultivation of B. pertussis, and because the metal slats would inherently bind to the toxin expression inhibitors, the reference anticipates the claimed invention.

Double Patenting

17. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

18. Claims 1-5 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 6,686,180. Although the conflicting claims are not identical, they are not patentably distinct from each other because the

claims of the patent represent a species of the presently claims genus of methods for the production of bacterial toxins. Because the claims of the current application are generic to those of the patent, the claims of the current application are therefore rejected for obviousness type double patenting.

Conclusion

19. No claims are allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Z. Lucas
Patent Examiner

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